Criteria for Screens—
Review of the EDSTAC Recommendations

Presentation to the EDMVS

July 23, 2002

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Purpose of Tier 1

- To distinguish chemical substances that interact with the endocrine system from those that do not.
- Upon completion of Tier 1 EPA and stakeholders should be able to accept the assignment that a chemical has (1) either low or no potential for EAT activity, (2) or that it has such potential.

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EDSTAC Criteria for Screens

- Detect all known modes of action for the endocrine endpoints of concern
- Include sufficient diversity among endpoints, permitting weight-of-evidence conclusions
- Maximize sensitivity to minimize false negatives
- Include a sufficient range of taxonomic groups among the test organisms to represent differences in endocrine system and metabolism
- Relatively fast and efficient

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Advantages of *In Vitro* Assays

- Sensitivity to low concentrations
- High specificity of response
- Low cost
- Small amount of chemical required
- Assays can be automated for high throughput
- Results can be used in conjunction with QSAR models
- Can be used for complex mixtures
- Reduces or replaces animal use

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Advantages of *In Vivo* Assays

- Account for absorption, distribution, metabolism and excretion
- Evaluate a broad range of mechanisms
- Provide a comprehensive evaluation of the whole endocrine system as a unit
- Generally well-accepted methods in toxicity testing
- Some endpoints are toxicologically relevant and have been used in hazard assessment
- Give comparative perspective to other endpoints of toxicity

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Meeting the Screening Criteria

- Detect all known modes of action for the endocrine endpoints of concern
  - Simple mechanistic screens do not exist for all modes of action, therefore it is necessary to include more complex multi-modal assays in tier
- Include sufficient diversity among endpoints, permitting weight-of-evidence conclusions
  - Multiple endpoints in in vivo assays
  - Redundancy among endpoints across assays

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Meeting the Screening Criteria

- Maximize sensitivity to minimize false negatives
  - In vitro mechanistic screens are highly sensitive
- Include a sufficient range of taxonomic groups among the test organisms to represent differences in endocrine system and metabolism
  - Include in vivo assay for fish; fish have different hormones; opposite end of vertebrate phylogeny
- Relatively fast and efficient
  - Maximize use of in vitro assays

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Screens vs. Biological Activity

	E	E-	A	A-	T	SSI	AI	5a	HPG
ER Binding	X	X							
AR Binding			X	X					
Steroidogen						X			
Aromatase							X		
Uterotrophic	X	X							
Pubertal fem	X	X			X	X	X		X
Hershberger			X	X					LH
Pubertal male	X			X	X	X		X	X
Adult male	X			X	X	X	(X)	X	X
Fish Reproductive	X	X	X	X	?	X	X		X
Frog Thyroid					X				

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Conclusions

- No single assay can, at this time, meet all of the criteria for a Tier 1 screen;
- Therefore, a battery approach must be taken.
- The battery to be efficient should consist of both *in vitro* and *in vivo* assays.

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